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Epithelial Cell-derived a Disintegrin and Metalloproteinase-17 Confers Resistance to Colonic Inflammation through EGFR Activation

Shimoda, M.[1]; Horiuchi, K.[1]; Sasaki, A.[1]; Tsukamoto, T.[2]; Okabayashi, K.[1]; Hasegawa, H.[1]; Kitagawa, Y.[1]; Okada, Y.[1]
[1]Keio University School of Medicine, Tokyo, Japan; [2]Fujita Health University School of Medicine, Aichi, Japan

Epithelial regeneration is a key process for the recovery from ulcerative colitis (UC). Here we demonstrate that a disintegrin and metalloproteinase-17 (ADAM17), a main sheddase for tumor necrosis factor (TNF)-α, is essential for defensive epithelial properties against UC by promoting epithelial cell growth and goblet cell differentiation in mouse and human. Mice with systemic deletion of *Adam17* developed severe dextran sulfate sodium-induced colitis when compared to mice with myeloid cell *Adam17* deletion or control littermates. ADAM17 was predominantly expressed by regenerating epithelia in control mice, and its loss or inhibition attenuated epidermal growth factor receptor (EGFR) activation, epithelial proliferation, mucus production and barrier functions. Conversely, ectopic EGFR stimulation promoted epithelial regeneration thereby partially rescuing the severe colitis caused by ADAM17 deficiency. In UC patients, epithelial ADAM17 expression positively correlated with both cell proliferation and goblet cell number. These findings suggest that maintaining ADAM17-EGFR epithelial signaling is necessary for the recovery from UC and would be beneficial to therapeutic strategies targeting ADAM17-mediated TNF-α shedding.